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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/974,760	10/09/2001	Shannon Roberts	MIC-005 (109272.150)	8318

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EXAMINER	
LAMBERTSON, DAVID A	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 09/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/974,760	ROBERTS ET AL.	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *77-135* is/are pending in the application.

4a) Of the above claim(s) *77-98 and 126-135* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *99-125* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Claims 77-135 are pending in the instant application. Applicant's election without traverse of Group II (claims 99-125) in the reply filed on July 1, 2004 is acknowledged. Claims 77-98 and 126-135 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Information Disclosure Statement

The information disclosure statements filed May 24, 2002, December 31, 2002 and October 8, 2003 have been considered, and a signed and initialed copy of the form PTO-1449s are attached to this Office Action. It is noted that references C2, C5, C13, C18, C23, C24 and C31-33 have not been provided because "these are books and are too voluminous to copy" (see the IDS filed May 24, 2002, first page). As such, these references have been lined through on the corresponding form PTO-1449 as "not considered."

Claim Objections

Claim 122 is objected to because of the following informalities: claim 122 refers to non-elected subject matter set forth in claim 77. It is recommended that the non-elected subject matter be removed from the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 122-124 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Specifically, the claims refer to a fungal strain (in specific instances an *A. terreus* fungal strain) comprising a mutated nucleic acid encoding a protein. While the nucleic acid itself shows the hand of man because it is isolated, the fungal cell reads on a strain that can appear in nature (particularly because the instantly claimed polynucleotide originates in *A. terreus*). Specifically, any fungal strain may contain a given point mutation in a particular gene; thus a fungal strain comprising a mutated nucleic acid can occur in a natural environment and represents non-statutory subject matter. It would be remedial to indicate that the fungal strain is recombinant in some manner (e.g., it recombinantly expresses a nucleic acid).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 99-119 and 121-125 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant claims an isolated nucleic acid molecule comprising a nucleic acid that encodes a protein comprising the amino acid sequence of SEQ ID NO: 91 having at least one of

a given number of amino acid changes. The claims read on a broad genus of proteins without an indication of a structure-function relationship. In particular, an infinite number of amino acid changes can be made in the protein encoded by the claimed polynucleotide; however, there is no indication of a functional activity for this infinite number of encoded polypeptides, thus there is no structure function relationship.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicants were in possession of the claimed genus. In the instant case, the specification does not sufficiently describe a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics.

As it regards the instant claims, there is no limit to the number of amino acid changes that can be introduced into the polypeptide encoded by the claimed polynucleotide, nor is there a recitation of a required functional activity that must be associated with the polypeptide encoded by the claimed polynucleotides. Thus, Applicant claims an infinite number of polynucleotide sequences by structure only, without any disclosed function for these claimed polynucleotides (and their respective polypeptides) or a known correlation between the structural elements and their function. The specification only provides teachings regarding a few polynucleotides with a limited number of point mutations, wherein the point mutations result in an increased regulatory activity of the encoded lovE polypeptide. The specification does not teach an infinite number of

polynucleotides that encode a polypeptide that necessarily has an increased regulatory activity relative to a wild-type lovE polypeptide. In fact, the skilled artisan would be unable to envision what number of amino acid changes could be made without a result in a loss of a desired activity (whatever that activity may be) because the instant specification does not teach how many mutations can be made without a loss of the desired activity. Thus, the skilled artisan cannot envision a sufficient number of embodiments of the instant invention from the instant specification.

The prior art does not provide sufficient information on the subject to overcome the deficiencies of the instant specification. There is no description in the prior art that allows one to envision an infinite number of polynucleotides encoding a polypeptide for which no function is ascribed by disclosing structural or functional features of the polynucleotide (or its corresponding encoded polypeptide) so that one of skill in the art could envision the claimed invention. Thus the skilled artisan cannot rely on the prior art to envision a sufficient number of embodiments of the instant invention to see that the applicant was in possession of the claimed genus.

Because neither the specification of the instant application or the prior art teaches a structure-function relationship for a representative number of the infinite number of polynucleotides claimed, the claims do not meet the Written Description requirement. As a result, the skilled artisan would not be able to envision the claimed invention by relying on the teachings of the prior art or the instant specification. Therefore applicant has not satisfied the written description requirement to show the skilled artisan that they were in possession of the claimed genus.

Claims 99-119 and 121-125 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), and the most relevant factors are indicated below:

Nature of the invention. The nature of the invention is a modified polynucleotide sequence that encodes a variant of the lovE regulatory protein. The lovE regulatory protein is involved in the biosynthesis of lovastatin, a secondary metabolite useful in treatment of conditions associated with improper levels of cholesterol. As set forth in the specification, the modified polynucleotides encode variant polypeptides that can be used to increase the production of lovastatin in host cells. The claimed polynucleotides, however, read on an infinite number of polynucleotides encoding an infinite number of polypeptides. It is also noted that there is no functional limitation on these polynucleotides (or their respective polypeptides), thus the claims read on virtually any polynucleotide (and encoded polypeptide) imaginable. Thus, in order to satisfy the enablement requirement the skilled artisan would need to be able to: (a) predictably

make any given nucleic acid encoding a lovE variant that (presumably, if this is the desired activity of the protein) has the ability to increase the production of lovastatin when expressed in a cell, and (b) be able to use the infinite number of polynucleotides encoding polypeptides that do not have a known activity.

Breadth of the claims. Because there is no limitation of the number of amino acid changes that can be encoded by the claimed polynucleotide sequence, the claim reads on a vast number of sequences for which no function is ascribed. Thus, the claims read on virtually any polynucleotide sequence, regardless of the activity or function of the polynucleotide sequence.

State of the art. In order to simplify the analysis of the state of the art, it is presumed that the desired activity of the polypeptide encoded by the claimed polynucleotide is an increased regulatory activity of the encoded variant lovE protein as it regards lovastatin biosynthesis. Concerning this presumed activity, the state of the art is silent with regard to the degree of mutation or the particular mutations that can be made to lovE while retaining its regulatory activity regarding lovastatin biosynthesis. Thus, the skilled artisan would be required to consult the instant specification to determine what particular mutations would result in an increased regulatory activity regarding lovastatin biosynthesis, as well as to what degree the lovE protein could be mutated (via its corresponding polynucleotide sequence) without a loss of activity.

As it regards percent homology between proteins, and the ability to retain function across non-identical proteins, the prior art indicates that it is unpredictable to predict functionality simply by homology. This was demonstrated by the conflicting publications of Scott *et al.* (*Nature Genetics* **21**: 440-443, 1999; see entire document; henceforth Scott) and Everett *et al.* (*Nature Genetics* **17**: 411-422, 1997; see entire document; henceforth Everett) regarding the

cloning and characterization of PDS. Everett initially identified and sequenced the protein, predicting based upon the sequence that the PDS gene product functioned as a sulphate ion transporter protein because of its similarity to a family of known sulphate ion transporters (see for example the Abstract and page 419, right column, second full paragraph). However, further characterization done by Scott indicated that PDS was not a sulphate ion transporter because it was unable to transport sulphate ions; rather, Scott identified that PDS was a chloride and iodide ion transporter (see for example the Abstract and page 440, the paragraph bridging the left and right columns to the second full paragraph). Scott further indicated that their results underscored the importance of establishing function even in the face of significant homology to proteins of known function (see for example page 441, left column, third full paragraph), thereby establishing that function based on homology is an unpredictable endeavor. Thus, the state of the art indicates that there is a demarcation between when a protein will lose a given activity. This is important in the instant case because of the unlimited number of mutations that can be made in the protein encoded by the claimed polynucleotide sequence; specifically, it establishes that the skilled artisan could not predict what level of mutation would be acceptable while still resulting in the (presumed) desired activity of an increased regulatory function regarding lovastatin biosynthesis, without specific teachings from the instant specification.

Number of working examples and Guidance provided by applicant. The instant specification describes a number of individual and compound (i.e., a combination of individual point mutations) point mutations that appear to have an effect of the ability of the encoded lovE protein to increase the production of lovastatin. However, this does not equate to the ability to change an unlimited number of amino acids (via mutating the encoding polynucleotide), while

still retaining the (presumed) activity of an increased regulatory function regarding the biosynthesis of lovastatin. While the skilled artisan would be able to make any of the various individual and compound point mutations described in the instant specification, the skilled artisan would be unable to make the infinite number of polynucleotides encoding a protein having the (presumed) desired activity of an increased regulatory function regarding the biosynthesis of lovastatin, without undue and unpredictable trial and error experimentation.

Unpredictability of the art and Amount of experimentation required. The instant claims require a great deal of trial and error experimentation in order for the skilled artisan to be able to make and use the invention.

First and foremost, because the invention reads on virtually any nucleic acid with no assignment of activity, the skilled artisan would necessarily have to determine the activity and a given use for every possible polynucleotide. Afterwards, the skilled artisan would then need to determine a use for said polynucleotide. This is an infinite amount of empirical experimentation.

Second, with regard to polynucleotides encoding proteins having the (presumed) desired activity of an increased regulatory function regarding the biosynthesis of lovastatin, the skilled artisan would be able to make and use any of the specific sequences containing the individual or compound mutations taught in the specification. However, the number of additional mutations that could be made remains unclear, and the claimed invention allows for an infinite number of such mutations. Thus, the ordinary skilled artisan would need to practice undue and unpredictable trial and error experimentation in order to determine how many mutations could be made relative to polynucleotide encoding the wild-type lovE polypeptide without disrupting the (presumed) desired activity.

Thus, it is clear that the instant claims, due to their breadth (encompassing virtually any polynucleotide), a lack of an ascribed function over the breadth of the claims (i.e., what activity must be maintained), the unpredictability of the art as it regards maintaining a given function over sequence similarity, and the limited teachings of the instant specification (describing only specific individual and compound point mutations), lack enablement over the full scope of the invention. The skilled artisan could not make any polynucleotide that has an increased regulatory function regarding lovastatin biosynthesis (presuming that to be the desired activity of the polypeptide encoded by the claimed polynucleotide), nor could the skilled artisan predictably use those polynucleotides that did not have such an activity. As a result, the indicated claims fail to meet the enablement requirement under 35 USC § 112, first paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 99-125 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 99 (and all of its dependent claims) recites the phrase "comprising an amino acid sequence of SEQ ID NO: 91 having at least one amino acid change." This phrase renders the claim indefinite because it is unclear how many amino acid changes can be introduced into SEQ ID NO: 91 before it is considered to no longer comprise SEQ ID NO: 91. For example, if every second amino acid or every second and third amino acid is changed (giving the sequence 50% and 33% homology to SEQ ID NO: 91, respectively), it is unclear if the sequence still reads on a

polypeptide comprising the sequence of SEQ ID NO: 91 having at least one amino acid change. While it is clear that the hypothetical sequences sequence have at least one amino acid change (and indeed many more), the fact that the sequences no longer resemble SEQ ID NO: 91 raises the question as to whether or not the sequences meet the limitations of the claim. This issue is also addressed above under 35 USC § 112, first paragraph, where it is set forth that the claim can read on any polynucleotide sequence, depending on when a sequence ceases to "comprise the amino acid sequence of SEQ ID NO: 91.

Claims 99 (and all of its dependent claims) recites the terms "Group X amino acid," wherein X represents a number from 1-6. This term is indefinite because the instant specification does not unambiguously define what amino acids fall into each Group. It is noted that the amino acids have been classified in multiple ways in the scientific literature, thus there is no certain definition that one amino acid is always in a particular "Group." Furthermore, the instant specification provides only a cursory definition of the terms on page 24, lines 15-23. Unfortunately, in this cursory definition, it is stated that the Groups "typically include" the indicated amino acids. Given that description, it is unclear what the groups are under atypical situations, which are also included within the definition of the Groups. As such, the metes and bounds of the claim have not been defined.

Claim 124 recites the limitation "fungal cell" in relation to claim 121. There is insufficient antecedent basis for this limitation in the claim because claim 122 is drawn to a nucleic acid, not a fungal cell.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following rejections are predicated on the following interpretations of the claims. First, it is noted that the mutations are defined as being present only with regard to SEQ ID NO: 91 (i.e., where a Phe at position 31 is changed), and that there are an unlimited number of mutations that can be made across the entire polynucleotide (and its encoded polypeptide). There is no indication of what position in any given polynucleotide (and its encoded polypeptide) necessarily corresponds to the recited positions for the mutations in SEQ ID NO: 91; thus, this positioning is relative and depends solely on the particular alignment that is chosen, which is arbitrary. Because any given polynucleotide can be aligned numerous ways with respect to SEQ ID NO: 91, every polynucleotide can align at some point to give a mutation from any one amino acid to each of the other 20 amino acids. As such, any polynucleotide can arbitrarily meet the limitation of having a point mutation relative to a given location in SEQ ID NO: 91. Second, since there is no limit to the number of mutations that can be present in the claimed sequence (it can have 0% sequence homology with SEQ ID NO: 91), any polynucleotide sequence will align with SEQ ID NO: 91 to give the claimed sequence. Finally, the instant claims read on a polynucleotide sequence having any (or no) function, there being no recitation of a functional requirement for the polynucleotide (or the polypeptide it encodes). Each of these interpretations

is within the metes and bounds of the claims, and supports the contention that any polynucleotide sequence will necessarily meet the limitations of the claims.

Claims 99 and 121-125 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,849,541 (see entire document; henceforth Vinci).

Vinci teaches the identification and cloning of triol polyketide synthase gene (TPKS) from *A. terreus* (see for example the Abstract). Significantly, at position 52, TPKS has the amino acid asparagine (see for example Figure 2), which (as exemplified in the instant specification) can be considered a Group 3 amino acid. Thus, due to the limitless changes allowed in the instantly claimed polynucleotides, and the arbitrary alignment of the TPKS and SEQ ID NO: 91 sequences at position 1 in each sequence, TPKS anticipates the claimed polynucleotide sequence. Vinci further teaches the expression of this sequence in various host cells, including bacterial, yeast (such as *S. cerevisiae*), mammalian and insect (see for example column 6, lines 38-41). In particular, Vinci exemplifies expressing the polynucleotide in *A. terreus* (see for example Examples 18-19). As such, Vinci anicipates the instantly claimed invention.

Claims 99-101 and 121-125 are rejected under 35 U.S.C. 102(e) as being anticipated by US 6,391,583 (IDS reference; see entire document; henceforth Hutchinson).

Hutchinson teaches a lovE polynucleotide and polypeptide sequence (see for example the Abstract), particularly SEQ ID NO: 8. Significantly, SEQ ID NO: 8 is highly homologous to SEQ ID NO: 91 of the instant specification; however, beginning at amino acid position 228 of

SEQ ID NO: 8 there is an insertion (see for example the sequence listing). This insertion causes a shift in the alignment of SEQ ID NO: 8 of Hutchinson and SEQ ID NO: 91 of the instant application, such that amino acid 389 of SEQ ID NO: 8 becomes a threonine, which (as exemplified in the instant specification) can be a Group 4 amino acid. Thus, given the limitless number of amino acid changes and the arbitrary alignment of SEQ ID NO: 8 (of Hutchinson) and SEQ ID NO: 91 (of the instant application) at amino acid position 1, Hutchinson teaches the claimed polynucleotide sequence. Furthermore, it is asserted that because Hutchinson teaches that SEQ ID NO: 8 is lovE, this polynucleotide will necessarily and inherently encode a polypeptide that increases the expression of a lovF gene in both an *A. terreus* and *S. cerevisiae* cell; this inherency is supported by the indication that the expression of such a sequence in these cells is designed to increase the production of lovastatin in the cells (see for example column 7, lines 30-35). It is additionally noted that Hutchinson teaches expressing SEQ ID NO: 8 in yeast cells (i.e., *S. cerevisiae*) and other fungi, preferably *A. terreus* (see for example column 7, lines 30-35). As such, Hutchinson teaches the invention as claimed.

Allowable Subject Matter

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (571) 272-0771. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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JAMES KETTER
PRIMARY EXAMINER